

Cross-Reference To The Related Application

Background of the Invention

[0003] 3-Amino-pyrrolidine derivatives can be manufactured in a manner known per se, for example as described in EP-A-O 218 249 starting from 1,2,4-trisubstituted butane derivatives such as e.g. tribromobutane or trihydroxybutane. The racemic derivatives can then, if desired, be converted by a racemate resolution into optically active 3-amino-pyrrolidine derivatives, as described in JP 09124595-A. A process for the manufacture of optically active 3-amino-pyrrolidine derivatives based on the conversion of 4-hydroxy-proline as described, for example, in J. Med. Chem. 1764(92), 35, gives optically active 3-aminopyrrolidine over 3 steps.

[0004] The known methods for the manufacture of 3-aminopyrrolidine derivatives as described, for example, in UK Patent No. 1,392,194, EP-A-o 391 169 and US Patent No. 4,916,141, are time consuming and lead to expensive intermediates. The interest in other processes for the manufacture of 3-amino-pyrrolidine derivatives, especially of optically active 3-amino-pyrrolidine derivatives, is therefore extremely high. Thus, Tomori et al. (Heterocycles, 1997, 1, 213-225) have synthesized (S)-3-(t-butoxycarbonylamino)-pyrrolidine from (S)-3-benzyloxycarbonylamino-1,4-dimethanesulfonyloxybutane by cyclization with excess allylamine and deallylation of the resulting (S)-1-allyl-3-(benzyloxycarbonylamino)pyrrolidine with palladium on charcoal. However, on a technical scale allylamine is unpractical, being a poisonous, inflammable and explosive liquid; also, palladium is an expensive catalyst.

[0005] As can be seen, there is a need for a practical, safe, technical scale synthetic method for the synthesis of 3-aminopyrrolidine derivatives. Such a synthetic method should be cost effective and able to be performed safely on a large scale.

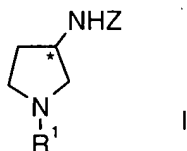
Summary of the Invention

[0006] It was now found that 3-amino-pyrrolidine derivatives, especially optically active 3-amino-pyrrolidine derivatives, can be safely manufactured in high yield on a technical scale by replacing allylamine with hydroxylamine or its acid addition salt, particularly the hydrochloride, which is cheap and much easier to handle, having none of the disadvantages. Further, being a solid, hydroxylamine hydrochloride is easily soluble in polar organic solvents such as tetrahydrofuran, ethanol, triethylamine or mixtures

thereof. The hydroxy group of the resulting N-hydroxy-3-protected-aminopyrrolidine is then removed by catalytic reduction with Raney nickel, which is a cheap catalyst.

Detailed Description of the Invention

[0007] In accordance with these findings, the invention is concerned with a process for the manufacture of 3-amino-pyrrolidine derivatives of the formula



wherein

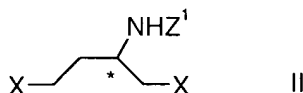
R¹ signifies hydrogen or an amino protecting group;

Z signifies hydrogen or an amino protecting group;

and

* represents a center of chirality,

which process comprises converting a compound of the formula



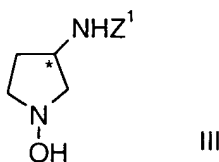
wherein

X signifies a protected hydroxy group;

Z¹ signifies an amino protecting group; and

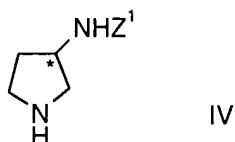
* has the above meaning,

in the presence of hydroxylamine or an acid addition salt thereof into the N-hydroxy-pyrrolidine derivative of the general formula



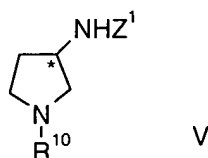
wherein Z¹ and * have the above meanings,

the N-hydroxy group of which is subsequently reduced to the secondary amine of the general formula

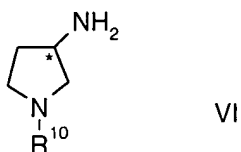


wherein Z¹ and * have the above meanings,

- 5 by hydrogenation with Raney nickel; and, if desired, protecting the secondary N¹ amino group by reaction with a compound of the formula R¹⁰X¹, in which R¹⁰ is an amino protecting group and X¹ is halogen or a leaving group, to yield a compound of the general formula



- 10 in which R¹⁰, Z¹ and * have the above meanings,
and, if desired, deprotecting the secondary 3-amino group by catalytic hydrogenation to yield a compound of the general formula



in which R¹⁰ and * have the above meanings.

- 15 [0008] Under the above definitions the term "protected hydroxy group" in the scope of the present invention encompasses ester groups, for example, sulfonates such as mesylate, tosylate, p-bromobenzenesulphonate or p-nitrobenzenesulphonate. These are especially groups which are cleaved off selectively under the reaction conditions for the
20 ring closure such that the amino protecting group Z in the 2-position is not liberated.

Mesylate and tosylate (mesyloxy and tosyloxy) are especially preferred protected hydroxy groups X.

[0009] The term "amino protecting group" in the scope of the present invention encompasses lower alkyl, benzyl, lower alkenyl, lower alkoxy carbonyl, lower alkenyloxy carbonyl, benzyloxy carbonyl and the like. t-Butoxycarbonyl, allyloxycarbonyl and benzyloxy carbonyl, particularly the latter, are especially preferred.

[0010] The term "leaving group" embraces halogen atoms, such as chlorine or bromine, and lower alkylsulfonyloxy or lower alkylphenylsulfonyloxy groups such as mesyloxy or tosyloxy, also anhydride residues of carbonic acid such as t-butoxycarbonyloxy.

[0011] The term "lower alkyl" in the scope of the present invention encompasses straight-chain and branched, optionally chiral hydrocarbon groups with 1 to 8 carbon atoms such as, for example, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, isopropyl, isobutyl, tert-butyl, 2-methylbutyl and the like. "Lower alkoxy" has analogous significance.

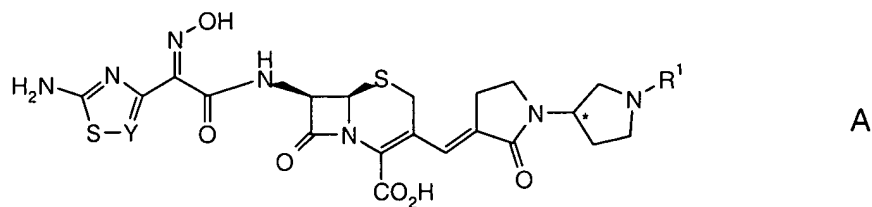
[0012] The term "lower alkenyl" encompasses olefinic, straight chain and branched groups with 2 to 8 carbon atoms such as vinyl, allyl, 3-butenyl, 1,3-butadienyl.

[0013] The terms "lower allyl", "lower alkoxy" and "lower alkenyl" keep their meanings in combinations e.g. with "carbonyl", e.g. t-butoxycarbonyl, allyloxycarbonyl.

[0014] In an especially preferred aspect of the process of the present invention optically active R-form of 2-(benzyloxy carbonylamino)-1,4-dimethanesulfonyloxybutane is

cyclized with hydroxylamine hydrochloride at about 0°C to the boiling point of the reaction mixture in a polar solvent such as tetrahydrofuran, ethanol, triethylamine or dimethylsulfoxide or a mixture thereof, quite preferably in triethylamine. Subsequently, the hydroxy group of the resulting N-hydroxy-3-protected pyrrolidine of formula III is
 5 reductively removed by hydrogenation with Raney nickel at room temperature in a hydrogen atmosphere. The resulting secondary amine of formula IV can subsequently be N-protected, preferably by t-butoxycarbonyl, by reaction with di-t-butyl-dicarbonate, preferably at room temperature. The benzyloxycarbonyl protecting group of the resulting di-protected product of formula V is expediently removed catalytically with
 10 hydrogen and palladium on charcoal, preferably at room temperature.

[0015] The resulting primary amine of formula VI is especially suitable for manufacturing vinylpyrrolidinone-cephalosporin derivatives of the general formula



wherein

Y signifies CH or nitrogen;

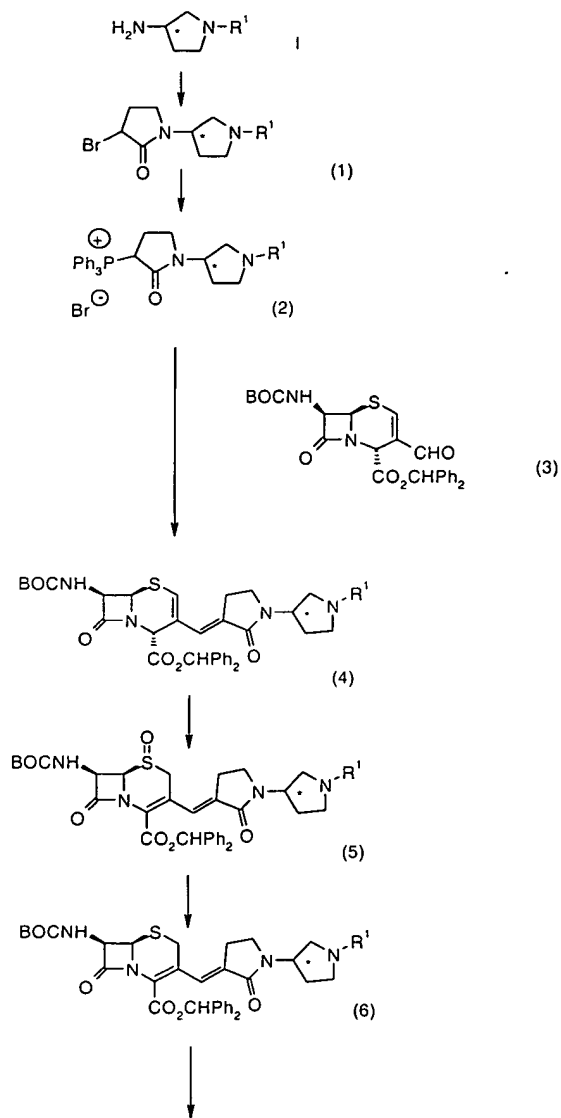
R¹ denotes hydrogen or an amino protecting group; and

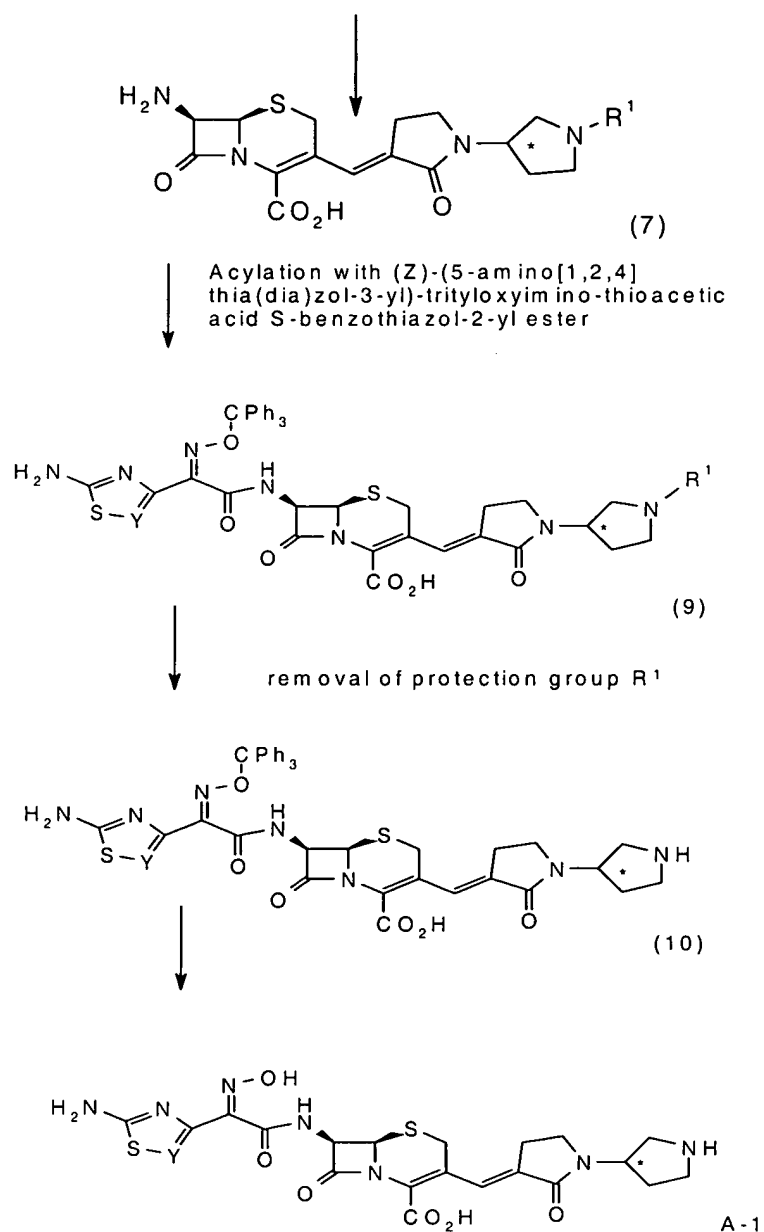
* denotes a center of chirality.

[0016] Compounds of formula A are cephalosporin derivatives having a high antibacterial activity, especially against methicillin-resistant strains of *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*.

[0017] Compounds of the general formula A can be produced as per EP-A-849 269 in accordance with Scheme I:

Scheme 1





[0018] In Scheme 1 Y, R¹ and * have the above significance; Ph is phenyl, BOC is
 5 t-butoxycarbonyl and CHPh₂ is benzhydryl.

[0019] For obtaining the compounds of the general formula A the 3-amino-pyrrolidine derivative of formula I are manufactured in accordance with the invention according to the method described above, thereafter reacted in accordance with Scheme 1 with 2-bromo-4-chlorobutanoyl chloride, and the N-substituted 3-bromo-2-pyrrolidone (1) so obtained is converted into the Wittig salt (2) which is reacted with the diprotected 3-ene cephalosporin (3). The resulting condensation product (4) is oxidized to the 5-sulfoxide (5) which is reductively isomerized with PBr_3 to the 2-ene cephalosporin (6), the latter is N-deprotected and acylated with the activated acyl derivative (8) to yield (9) which is deprotected in two steps to yield (10) and finally the end product of formula A.

[0020] The following Examples serve to illustrate the invention.

Example 1

(R)-3-(Benzyloxycarbonylamino)-N-hydroxy-pyrrolidine.

[0021] (R)-2-(Benzyloxycarbonylamino)-1,4-dimethanesulfonyloxybutane (2.0 g; 5.06 mmol) was dissolved in a Et_3N /DMSO mixture (1:1, 20 ml). Hydroxylamine hydrochloride (1.4 g; 20.2 mmol) was added and the mixture was heated at 60°C over night. The mixture was poured in aqueous HCl (the pH was adjusted to pH=6 with NaHCO_3) and extracted twice with AcOEt. The organic phase was washed with water and dried over Na_2SO_4 . The solids were filtered off and the solvent was removed. A light yellow oil (1.4 g, purity 73%) was obtained (yield: 85%). The crude title compound was used as is.

Example 2

(R)-3-(Benzyloxycarbonylamino)-N-(t-butoxycarbonyl)-pyrrolidine.

[0022] The crude (R)-3-(benzyloxycarbonylamino)-N-hydroxy-pyrrolidine obtained
5 above (1.4 g) was dissolved in ethanol (10 ml). Raney nickel (about 2 g) was added to
this mixture. The reaction was degassed under reduced pressure and hydrogen supply
(three times) and subsequently put under hydrogen atmosphere (1 bar). The reaction
was over after 6 hours, yielding crude (R)-3-(benzyloxycarbonylamino)-pyrrolidine
10 which was further processed in situ, in that di-tert-butyl dicarbonate (1.0 g, 4.58 mmol)
was added; the mixture was stirred for one hour. The solvent was removed and the
residue taken up in an n-hexane/AcOEt mixture (1:1, 20 ml) and filtered through a
silicagel pad. The silica was washed with n-hexane/AcOEt mixture (1:1; 250 ml). The
organic phases were evaporated. The compound was obtained as a colorless oil (1.125 g;
15 yield 81%) in good purity, i.e. at least 90 - 95 %, rendering the compound sufficiently
pure for further reaction, e.g. in Example 3.

NMR: (CDCl₃; 300 MHz): 7.34 (m; 5H); 5.1 (s(broad); 2H); 4.83 (m(broad); 1H); 4.22
(m(broad); 1H); 3.60 (dd; 1H); 3.41 (m(broad); 2H); 3.18 (m(broad); 1H); 2.12 (m; 1H);
1.82 (m(broad); 1H); 1.45 (s; 9H).
20 MS: (M+H⁺): 321.3 (M+NH₄⁺): 338.2

[0023] Example 2 may also be carried out under pressure in a pressure reactor at a
pressure range of 1 to 50 kg, more preferred 1 to 20 kg, most preferred at a pressure of
3.8 kg. Further the reaction may be carried out at a temperature between 20 °C and 100
25 °C, more preferred 40 °C to 60 °C, most preferred the reaction may be carried out at a
temperature of 55 °C.

Example 3

(R)-3-Amino-N-(t-butoxycarbonyl)-pyrrolidine.

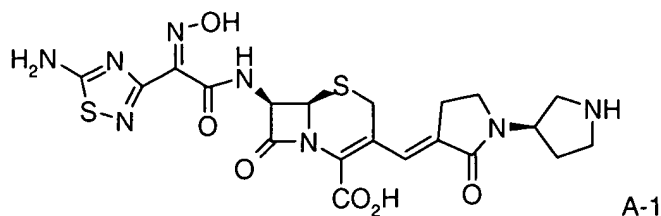
[0024] (R)-3-(Benzyloxycarbonylamino)-N-(t-butoxycarbonyl)-pyrrolidine (300 mg) was dissolved in ethanol (5 ml). Palladium on charcoal 10% (20 mg) was added. The reaction was degassed three times and put under hydrogen atmosphere (1 bar). The reaction was over after 2 hours. The solvent was removed, the residue was taken up in ethyl acetate (5 ml) and filtered through a silica gel pad. The silica was washed with ethyl acetate (50 ml). The organic phases were evaporated. The desired (R)-3-Amino-N-(t-butoxycarbonyl)-pyrrolidine was obtained as a colorless oil in a quantitative yield (175 mg).

NMR: (CDCl₃; 300 MHz): 3.6-3.3 (m(broad); 3H); 3.05 (m(broad); 1H); 2.29 (s(broad); 2H); 2.05 (m; 1H); 1.66 (m(broad); 1H); 1.46 (s; 9H).

MS: (M+H⁺): 187.3

[0025] Example 3 may also be carried out under pressure in a pressure reactor at a pressure range of 1 to 50 kg, more preferred 5 to 40 kg, most preferred at a pressure of 20 kg. Further the reaction may be carried out in the presence of an acid (after the addition of Pd/C), such as acetic acid, HCl or perchloric acid. Most preferred perchloric acid is used.

[0026] The (R)-3-amino-N-(t-butoxycarbonyl)-pyrrolidine can be utilized in Example 2 of EP-A-o 849 269 instead of the N-allyloxycarbonyl derivative and subsequently in Examples 3-11 to yield (6R,7R)-7-[(Z)-2-(5-amino-[1,2,4]thiadiazol-3-yl)-2-hydroxyimino-acetyl-amino]-8-oxo-3-[(E)-(R)-2-oxo-[1,3']bipyrrolidinyl-3-ylidenemethyl]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid of the formula



Example 4

[0027] A 200 l reactor was charged with 27 l of dimethylsulfoxide, 9.5 kg of (R)-2-
 5 (benzyloxycarbonylamino)-1,4-dimethanesulfonyloxybutane and 6.68 kg of
 hydroxylamine hydrochloride and the reaction mixture stirred at room temperature to
 suspend. 27 l of triethylamine were added slowly, whereupon the temperature rose to 45
 - 50 °C. The reaction mass was maintained at 55 °C for four hours. The reaction was
 monitored by NMR or HPLC (high performance liquid chromatography). Subsequently
 10 the reaction mixture was cooled to room temperature.

[0028] Separately a solution was prepared with 100 l of water at 0 °C containing 14.2 l of
 concentrated aqueous hydrochloric acid. The above reaction mass was added to this
 solution and the pH value checked to 1.0 to 1.5. The aqueous layer was washed twice
 15 with each 10 l of 1:1 ethyl acetate and n-hexane and neutralized with 15 kg of sodium
 bicarbonate. The reaction mixture was stirred for 30 minutes and the pH checked to
 about 7.0 - 7.5. The aqueous layer was extracted three times with 15 l of ethyl acetate
 each time. The combined organic phases were washed twice with each 15 l of water
 followed by 10 l of brine (saturated aqueous sodium chloride solution).

20 [0029] The solvent was evaporated at reduced pressure, at the end of which the oily
 residue was stripped with 10 l of n-hexane. The n-hexane was evaporated off, n-hexane
 added again and the mixture stirred to precipitate the product. The crude (R)-3-

(Benzyloxycarbonylamino)-N-hydroxy-pyrrolidine was filtered off and used directly in example 5. The white solid obtained changed to yellow upon storage.

[0030] Yield 4.6 - 5.0 kg (80 - 85 %) having a purity of more than 95 %.

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Example 5

[0031] A 50 l autoclave was charged with 22.5 l of ethanol, 4.5 kg of (R)-3-(benzyloxycarbonylamino)-N-hydroxy-pyrrolidine and 1.35 kg of Raney nickel. The autoclave was put under hydrogen atmosphere (50 psi = 3.5 bar) and stirred for four hours. The reaction was monitored by HPLC and TLC.

[0032] After reaction the catalyst was filtered off and the solvent removed by evaporation at reduced pressure. The residue, crude (R)-3-(benzyloxycarbonylamino)-pyrrolidine, was dissolved in 20 l of ethanol followed by 4.15 kg of di-tert-butyl dicarbonate. The reaction mixture was stirred at room temperature for two hours, the reaction being monitored by HPLC and TLC. The solvent was evaporated off at reduced pressure, the reaction mixture being stripped twice by the addition of 2 l of toluene each time.

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[0033] 5.7 kg of crude (R)-3-(benzyloxycarbonylamino)-N-(t-butoxycarbonyl)-pyrrolidine was obtained as a yellowish oily residue, which was purified by dissolution, in a 20 l reactor, in 11.4 l of methylene chloride followed by 2.85 kg of silica gel and 57 g of charcoal. The reaction mixture was stirred for two hours at room temperature. The solids were filtered off and washed thoroughly with 10 l of methylene chloride. The

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combined organic layers were evaporated at reduced pressure, yielding 5.1 kg of (R)-3-(benzyloxycarbonylamino)-N-(t-butoxycarbonyl)-pyrrolidine as a colorless oil.

Example 6

5 [0034] An autoclave was charged with 51 l of ethanol, 5.1 kg of (R)-3-(benzyloxycarbonylamino)-N-(t-butoxycarbonyl)-pyrrolidine, 0.51 g of 5 % palladium-on-carbon and 0.5 l of perchloric acid. The autoclave was put under hydrogen atmosphere (100 psi = 7 bar) for one hour, the reaction being monitored by NMR. After
10 completion of the reaction the catalyst was filtered off and the solvent removed under reduced pressure.

[0035] The oily residue was dissolved in 10 l of ethyl acetate and the organic layer washed with 10 l of water, followed by 10 l 10 % aqueous sodium carbonate solution. The
15 organic phase was dried over sodium sulfate and the solvent removed by evaporation under reduced pressure. 2.5 kg of (R)-3-Amino-N-(t-butoxycarbonyl)-pyrrolidine was obtained as a colorless oil.

[0036] The NMR spectrum is identical with that reported under Example 3.

20 [0037] All references discussed throughout the above specification are herein incorporated in their entirety by reference for the subject matter they contain.

[0038] It should be understood, of course, that the foregoing relates to preferred
25 embodiments of the invention and that modifications may be made without departing from the spirit and scope of the invention as set forth in the following claims.